EVIDENCE ON THE DEVELOPMENTAL AND REPRODUCTIVE TOXICITY OF PROPACHLOR

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Propachlor

- Herbicide
- Solid at room temperature, MW 211.7D
- Used in agriculture in U.S. and other countries
- Not registered or used in California

Pharmacokinetics of propachlor

- Rapid absorption, distribution, metabolism, excretion
- Little tissue retention
- Complex metabolism, 11 metabolites identified
- Excreted mainly in urine

Non-developmental or reproductive toxicities

- Relatively low acute toxicity (rat oral LD_{50} 1,800 mg/kg)
- Severe eye irritant in rabbits
- Chronic and subchronic studies: reduced food consumption and body weight or weight gain, liver hypertrophy, reduced kidney weight, stomach lesions
- Palatability in feed at high concentrations considered a problem

Rabbit developmental toxicity study: Schardein 1984, Keller 1987

- New Zealand White rabbits, gd 7-19, gavage at 0, 5, 15, or 50 mg/kg/d
- No adverse maternal effects
- Increased pre- and post-implantation losses at 15 and 50 mg/kg/d
- Reduced litter sizes at 15 and 50 mg/kg/d
- Increased malformations (mainly skeletal) in all propachlor treated groups

Rabbit developmental toxicity studies: Adam 1992, Mercieca 1992

- Range finding study:
  New Zealand White rabbits, gd 7-19,
  gavage at 0, 25, 75, 125, 175, or 225 mg/kg/d
- Maternal deaths at 125, 175, and 225 mg/kg/d
- Lost body weight during dosing at 125, 175 mg/kg/d
- No developmental effects observed

Rabbit developmental toxicity studies: Adam 1992, Mercieca 1992

- Main study:
  New Zealand White rabbits, gd 7-19,
  gavage at 0, 5.8, 58, or 116.7 mg/kg/d
- Maternal deaths at 116.7 mg/kg/d
- Maternal food consumption reduced, body weight lost during dosing period at 116.7 mg/kg/d
- Early and late resorptions higher, litter size smaller, fetal weight lower at 116.7 mg/kg/d
- Bent hyoid arch increased at 116.7 mg/kg/d

Rat developmental toxicity studies: Suba 1982

- Range-finding study:
  Sprague-Dawley rats, gd 6-19, gavage
  at 0, 100, 200, 400, 600, or 800 mg/kg/d
- All females died at 400, 600, and 800 mg/kg/d
- Body weight and weight gain lower at 100 and 200 mg/kg/d
- Pre-implantation losses higher, litter size lower at 100 and 200 mg/kg/d.

Rat developmental toxicity studies: Suba 1982

- Main study:
  Sprague-Dawley rats, gd 6-19,
  gavage at 0, 20, 60, or 200 mg/kg/d.
- Maternal body weights and weight gains slightly lower at 60 and 200 mg/kg/d.
- No adverse developmental effects.

Rat reproductive toxicity study: Groya 1986

- Male and female Fisher 344 rats, two generations, in food at 0, 0.3,3.0, or 30 mg/kg/d.
- No female deaths attributable to propachlor.
- Reduced F1 female food consumption at 30 mg/kg/d.
- Maternal body weights similar among groups.
- No adverse developmental effects attributable to propachlor treatment.

Rat reproductive toxicity study: Lemen & Thake 1995

- Male and female Sprague-Dawley rats, two generations, in food at 0, 100, 1,000 or 2,500/5,000 (males/females) ppm.
- F0 female food consumption and body weights reduced at 1,000 and 5,000 ppm.
- F0/F1 litter size and pup birth weight reduced at 5,000 ppm.

Rat reproductive toxicity study: Lemen & Thake 1995 cont.

- F1 pup growth during lactation severely reduced at 5,000 ppm. Pup survival after weaning low: group terminated.
- F1 generation: 0, 100, 1,000 ppm groups.
- F1 female food consumption and body weight reduced at 1,000 ppm.
- F1/F2 litter size similar among groups.
- F1/F2 birth weight lower at 1,000 ppm.

Rat reproductive toxicity study: Groya 1986

- Male and female Fisher 344 rats, two generations, in food at 0, 0.3, 3.0, or 30 mg/kg/d.
- No female deaths attributable to propachlor.
- Reduced F1 female food consumption at 30 mg/kg/d.
- Maternal body weights similar among groups.
- F0/F1 mating: reduced fertility at 3.0 mg/kg/d.
- F1/F2a mating: reduced fertility at 3.0, 30 mg/kg/d.
- F1/F2b mating: fertility similar among groups.

Rat reproductive toxicity study: Lemen & Thake 1995

- Male and female Sprague-Dawley rats, two generation, in food at 0, 100, 1,000 or 2,500/5,000 (males/females) ppm.
- F0 female food consumption and body weights reduced at 1,000 and 5,000 ppm.
- F0/F1 mating fertility similar among groups.
- F0/F1 litter size and pup birth weight reduced at 5,000 ppm.

Rat reproductive toxicity study: Lemen & Thake 1995 cont.

- F1 pup growth during lactation severely reduced at 5,000 ppm. Pup survival after weaning low: group terminated.
- F1 generation: 0, 100, 1,000 ppm groups.
- F1 female food consumption and body weight reduced at 1,000 ppm.
- F1/F2 no adverse effect on fertility.
- F1/F2 litter size similar among groups.
- F1/F2 birth weight lower at 1,000 ppm.

Female reproductive organ weights and pathology

- Reproductive studies in rats (2).
- Subchronic and/or chronic studies in rats (4), mice (3), and dogs (2).
- No adverse effects on ovarian or other female reproductive organ weights or pathology.

Rat reproductive toxicity study: Groya 1986

- Male and female Fisher 344 rats, two generations, in food at 0, 0.3,3.0, or 30 mg/kg/d.
- No male deaths.
- Reduced F1 male food consumption and body weight at 30 mg/kg/d.
- F0/F1 mating: reduced fertility at 3.0 mg/kg/d.
- F1/F2a mating: reduced fertility at 3.0, 30 mg/kg/d.
- F1/F2b mating: fertility similar among groups.

Rat reproductive toxicity study: Lemen & Thake 1995

- Male and female Sprague-Dawley rats, two generation, in food at 0, 100, 1,000 or 2,500/5,000 (males/females) ppm.
- Male death: 1 F0 at 2,500 ppm, 1 F1 at 1,000 ppm.
- F0 male food consumption and body weights reduced at 1,000 and 2,500 ppm.
- Fertility in F0/F1 mating similar among groups.
- F0/F1 litter size at birth reduced at 2,500 ppm.

Rat reproductive toxicity study: Lemen & Thake 1995 cont.

- F1 pup growth during lactation severely reduced at 2,500 ppm. Pup survival after weaning low: group terminated.
- F1 generation: 0, 100, 1,000 ppm groups.
- F1 male food consumption and body weight reduced at 1,000 ppm.
- F1/F2 no adverse effect on fertility.
- F1/F2 litter size similar among groups.

Male dominant lethal study: Naylor 1994

- Male Sprague-Dawley rats treated for 10 weeks plus two rounds of mating, in food at 0, 300, 1,000, or 2,500 ppm.
- Food consumption and body weight reduced in the 1,000 and 2,500 ppm groups.
- Fertility, implantations, resorptions, and live litter size were similar among groups (I.e. no dominant lethal effects).

Male testicular pathology

- Studies showing no testicular pathology:
- Rat reproductive (2)
- Rat male dominant lethal (1)
- Rat chronic or subchronic (3)
- Mouse chronic or subchronic (3)
- Dog chronic or subchronic (2)

Testes weights

- Several studies in rats, mice and dogs reported results for male testes weights.
- In some studies, no effect. Some studies increased testes weights, some studies reduced testes weights.

Summary: developmental toxicity

- Schardein 1984, Keller 1987
  Rabbit developmental study observed developmental toxicity in absence of maternal toxicity at 15 and 50 mg/kg/d.
- Adam 1992, Mercieca 1992
  Rabbit developmental study did not observe developmental effects at 5.8 or 58 mg/kg/d. At 116.7 mg/kg/d, both maternal and developmental effects observed.

Summary: developmental toxicity cont.

- Suba 1982
  Rat developmental studies observed no developmental effects at doses below maternally lethal doses.

Summary: developmental toxicity cont.

- Groya 1986
  Rat reproduction study observed no developmental effects at up to 30 mg/kg/d in food.
- Lemen and Thake 1995
  Rat reproduction study observed reduced live litter size and birth weight in presence of maternal toxicity at 400 mg/kg/d in food. Also reduced pup growth during lactation at 400 mg/kg/d.

Summary: female reproductive toxicity

- Groya 1986
  Rat reproduction study observed inconsistent reductions in fertility at 3.0 and 30 mg/kg/d.
- Lemen and Thake 1995
  Rat reproduction study observed maternal toxicity at 400 mg/kg/d.
  No effect on fertility at up to 400 mg/kg/d.
  Reduced litter size at birth, birth weight, and pup growth during lactation at 400 mg/kg/d.

Summary: female reproductive toxicity cont.

- Numerous studies observed no effect on female reproductive organ pathology or weight.

Summary: male reproductive toxicity

- Groya 1986
  Rat reproduction study observed inconsistent reductions in fertility at 3.0 and 30 mg/kg/d.
- Lemen & Thake 1995
  Rat reproduction study observed male systemic toxicity at 70 and 166 mg/kg/d.
  No effect on fertility at up to 166 mg/kg/d.
  Reduced litter size at 166 mg/kg/d.

Summary: male reproductive toxicity cont.

- Naylor 1994
  Rat male dominant lethal study observed male systemic toxicity at 44 and 112 mg/kg/d. No effect on fertility, implantations, resorptions, or live litter size (i.e. no dominant lethal effects).

Summary: male reproductive toxicity cont.

- Numerous studies with propachlor observed no effect on spermatogenesis (gross and/or microscopic examination).
- Some studies observed no effect, others observed increased or decreased testes weights.